in that it is black letter law that applicants need not know how their invention works. An amendment has been provided correlating the preamble with a result.

Claims 4 and 9 are said to be indefinite is not indicating the location of the NF-AT3. Applicants have amended claim 4 as suggested by the examiner.

III. Rejection Under 35 U.S.C. §112, First Paragraph

A. Written Description

Claims 1, 4 and 9 are rejected for alleged lack of written description. According the examiner, applicants have provided an insufficient description of potential inhibitors to support the genus being claims. Applicants traverse.

The examiner analogizes to the Federal Circuit's decision in *The Regents of the University of California v. Eli Lilly*, which held that generic claims to mammalian insulin genes were not supported by the patentees' reporting of the rat sequence, and no others. First, applicants submit that a DNA is a vastly different chemical species than a DNA. The analogy to molecules that bind NF-AT3 is, therefore, dubious at best. Second, unlike the *Lilly* case, where a single species was held inadequate to support a genus, the present specification provides at least three different types of molecules – single chain antibodies, GATA4 mimetics, and small molecules. Thus, the genus is far better supported here than in *Lilly*. Third, applicants not that, at the time the present application was filed, the literature reported small molecule inhibitors of NF-AT3, dithiocarbamates (DTC's). Martînez-Martînez *et al.*, *Mol. Cell. Biol.* 17(11):6437-6447 (1997). Together, this creates a very different situation than the *Lilly* case.

The examiner goes on to argue that the disclosure "fails to describe the common attributes or characteristics that identify members of the genus." This is not true – the defining

characteristic is inhibition of NF-AT3 activity. Just because there is not ***structure*** in common does not mean that the genus is improper. Furthermore, the examiner's conclusion that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe ... the genus as broadly claimed" is unsupported by any evidence, save the examiner's opinion. This is improper.

The examiner also attacks the discussion of GATA4-based inhibitors on the grounds that the binding site on GATA4 for NF-AT3 "is not disclosed in the application, nor is it known in the art at the time the invention was made." This also is incorrect. The examiner is directed to Example 3, which clearly defines a region of GATA4 that is sufficient to interact with NF-AT3. Thus, this description is far more important than the examiner has admitted.

In sum, applicants submit that they have described an important aspect of cardiac biology – that NF-AT3 is a key player in hypertrophic signaling. It is, therefore, sufficient to describe methods of treatment for cardiac hypertrophy that focus more on the desired activity of the agents, and less on their structure. To hold otherwise would be to rob applicants of the opportunity to secure the property right they deserve for their contribution. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. Enablement

The examiner, in addition to advancing the written description rejection discussed above, has also rejected claim 1, 4 and 9 and lacking an enabling disclosure. The examiner provides the following points of contention. First, it is noted that the specification contains no treatment of transgenic mice with NF-AT3 inhibitors. Second, it is argued that it is unclear that NFAT3 is actually expressed in heart. Third, assuming heart expression, the examiner questions whether

NF-AT3 is translated into protein in heart muscle. Fourth, assuming translation, the examiner next raises an issue regarding NF-AT3 binding to GATA4 *in vivo*. Fifth, it is argued that the failure to define the location on NF-AT3 of small molecule inhibitor binding, as well as the dearth of information on the linearity of the site, precludes enablement. Sixth, focusing only on the antibody disclosure, the examiner takes the position that intracellular targeting of NF-AT3 could not be achieved. Applicants respectfully traverse each of these issues, and the rejection as a whole.

First, it is well established that examples are not required to prove up enablement, so long as the invention may be practiced without undue experimentation. *In re Borkowski*, 164 USPQ 642 (CCPA 1970). Rather, it is the examiner's burden to show that the disclosure necessitates undue experimentation. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). As will be discussed in the following paragraphs, the examiner's "proof" falls short of that needed to establish *prima facie* non-enablement.

Second and third, the issue of transcription and translation of NF-AT3 in intact cells is, in fact, a non-issue. As demonstrated in the attached abstracts, there is considerable evidence that NF-AT3 (a.k.a. NFATc4) is expressed in cardiac myocytes (Ichida & Finkel, 2001; Xia *et al.*, 2000). Thus, there can be little question that NF-AT3 is both transcribed and translated in cardiac muscle cells.

Fourth, the examiner's questioning of GATA4/NF-AT3 binding *in vivo* is not warranted. While there is no definitive proof of *in vivo* binding, Suzuki *et al.* (1999) demonstrated that GATA4 DNA binding and NF-AT activity show similar kinetics when cells are induced with AngII. While not technically *in vivo*, such a study lends further credibility to the data provided in Example 3.

Fifth, applicants submit that the specification, while not necessarily providing a specific location for inhibitor binding, provides a ***possible*** site in identifying the GATA4 interaction domain. Example 3 clearly defines the Rel homology domain has facilitating NF-AT3 binding to GATA4. Moreover, applicants need not ***know*** anything about the site to enable their methods, only that a small molecule inhibitor (*e.g.*, a DTC) actually functions as an inhibitor.

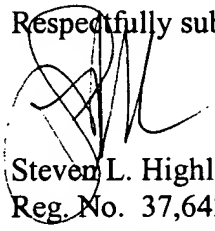
Sixth, and finally, applicants submit that the examiner is unnecessarily focusing the antibody disclosure to argue that appropriate targeting cannot be achieved. For example, the use of GATA4 mimetics and DTC's do not suffer from the perceived shortcomings of antibodies. In addition, it is well known that nuclear targeting signals can facilitate transport of proteins back into the nucleus. Thus, one may be presented with hurdles in developing a given therapeutic, there are means to address such problems. Furthermore, the generalized discussion of stability, half-life, proteolytic degradation, tissue penetration, circulation to target areas, *etc.*, such arguments can be made against almost any therapeutic approach. However, there are ways to address each of these issues, such as encapsidation, localized administration, or modification. In sum, this litany of potential problems, just like each of the preceding points, is an insufficient grounds for finding lack of enablement.

Therefore, it is respectfully submitted that the present claims are in fact enabled by the instant specification. As such, applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Davis have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: January 9, 2002

APPENDIX A: MARKED UP COPY OF CLAIMS

1. (Amended) A method of treating hypertrophy in a [cardiomyocyte cell] subject comprising the step of inhibiting the function of NF-AT3 in a cardiomyocyte, wherein inhibition of NF-AT3 function inhibits hypertrophic gene expression, thereby treating hypertrophy.

4. (Amended) The method of claim 1, wherein inhibiting the function of NF-AT3 comprises contacting [NF-AT3] said cardiomyocyte with an agent that binds to and inactivates NF-AT3.

9. The method of claim 4, wherein the agent that binds to and inactivates NF-AT3 is an antibody preparation or a small molecule inhibitor.